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Impact of HCV eradication following direct-acting antivirals on liver stiffness measurement: a prospective longitudinal study

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Abstract

Background and study aims Egypt has been a pioneer in implementing a nationwide HCV screening and treatment program. Assessment of liver fibrosis after HCV eradication is important. The value of liver stiffness measurement (LSM) for this purpose is still debated. The aim of this prospective longitudinal study was to assess LSM evolution after HCV eradication.

Patients and methods One-hundred and three HCV patients, treated with a standard DAA regimen (sofosbuvir/daclatasvir for 3 months), underwent LSM before and 24 weeks after the end of treatment. Patients were classified into 3 groups according to baseline LSM (Baveno VI): group 1: patients without compensated advanced chronic liver disease (cACLD) (*LSM* < 10 kPa); group 2: patients with suspected cACLD (LSM 10–15 kPa); and group 3: patients with likely cACLD (*LSM* > 15 kPa).

Results The characteristics of patients were as follows: mean age 55 ± 10 years, males 48.5%, and *BMI* 26.31 ± 3.33 kg/m^2. All patients were Child–Pugh score A and achieved SVR at W24. A significant LSM decrease was observed at W24 compared to baseline: all patients: 5.8 vs. 8.8 kPa, $p = 0.002$; group 1: 4.75 vs. 6.0 kPa, $p = 0.0001$; group 2 11.9 vs. 12.6 kPa, $p = 0.042$; and group 3: 24.2 vs. 28.3 kPa, $p = 0.0001$. Group 1 had the highest LSM decline (23.83%), followed by group 3 (14.3%) and group 2 (8.4%).

Conclusion HCV eradication was associated with a significant LSM decrease in all groups of patients. This is likely related to improvement of fibrosis, but its relation to improvement of necro-inflammation cannot be excluded. Longer follow-up of fibrosis in these patients is needed.

Keywords HCV, Sofosbuvir/daclatasvir, Sustained virological response, Compensated advanced chronic liver disease, Liver stiffness measurement, Transient elastography

Introduction

Chronic hepatitis C virus (HCV) infection is a major global health problem affecting 1% of the world population [1]. Egypt has the highest HCV prevalence in the world, with 7% of adults (15–59 years old) HCV RNA positive [2]. Egypt has managed to implement a successful nationwide HCV screening and treatment program that enabled the treatment of about 4 million patients. By screening 49.6 million people over a period of 7 months,

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2.2 million HCV-seropositive patients were identified and referred for evaluation and treatment. It is considered the largest disease screening campaign ever [3]. Sofosbuvir plus daclatasvir (Sof/Dac) is the most common direct-acting antiviral (DAA) regimen used in Egypt for HCV treatment.

Staging liver fibrosis after SVR in HCV patients with compensated advanced chronic liver disease (cACLD) is critical as they still have a residual risk of liver-related complications. Regression of fibrosis in HCV patients with cACLD has been described after sustained virological response (SVR) in patients treated with interferon-based therapies [4]. With the advent of direct-acting antivirals (DAAs) leading to SVR in most HCV patients with cirrhosis [5], regression of fibrosis will likely become even more common. However, post-SVR liver biopsies are not the standard of care.

Noninvasive tests are now widely used as first-line tests to assess liver fibrosis before DAA treatment in HCV patients and are recommended by international guidelines [6]. The most validated and widely used technique is transient elastography (TE), a point-of-care procedure allowing liver stiffness measurement (LSM) [7]. A recent meta-analysis, including 2934 HCV patients, reported a significant LSM decrease 24–48 weeks following the end of therapy in SVR patients, whereas no change was observed in non-SVR patients [8]. However, most of the studies included in this meta-analysis were retrospective, interferon-based, with small sample sizes, and short follow-up following SVR. Whether LSM can capture regression and stage of fibrosis following SVR in HCV patients with cACLD treated with DAA is an important issue.

The aim of the study was to evaluate the effect of sustained virological response 24 weeks following the end of treatment (SVR 24) on LSM, using TE, in HCV patients treated with DAA (Sof/Dac).

Patients and methods

This study was a prospective longitudinal study conducted on 103 patients with chronic HCV infection (positive HCV antibody test and positive HCV RNA) in the outpatient clinic of hepatology and gastroenterology at Theodor Bilharz Research Institute (TBRI), Egypt. Prior to inclusion in this study, all patients signed a written informed consent, and the institutional ethical committee in TBRI approved the study. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

The following patients were excluded: those with baseline body mass index (BMI) > 35 kg/m^2, cirrhotic patients with Child–Pugh score more than 9 (class C), patients with platelet counts < 50,000/mm^3, and those with ascites, HCC, or any hepatic focal lesion. Patients with combined HCV/hepatitis B virus infection and/or bilharziasis diagnosed by serology were also excluded. Patients with history of significant alcohol intake and/or intravenous drug abusers and those who received other direct-acting antiviral (DAA) regimens were also excluded. Treatment-eligible patients received sofosbuvir 400 mg and daclatasvir 60 mg daily for 12 weeks (Sof/Dac). Patients were closely monitored during treatment and followed until week 24 following the end of treatment.

Before treatment, all patients were subjected to a full medical history and a thorough clinical examination. The patients were asked about previous treatment for HCV and for features suggestive of decompensated cirrhosis. Blood samples were obtained from all patients. The following parameters were determined: complete blood count, liver function tests, kidney function tests, HBsAg, alpha-fetoprotein, pregnancy test for females at childbearing age, and abdominal ultrasonography. A quantitative measurement of HCV serum load was performed by real-time PCR, and it was repeated 12 and 24 weeks following the end of treatment to detect SVR 12 and SVR 24.

LSM was performed using transient elastography (TE) (FibroScan, Echosens, Paris, France) by an experienced operator. Only results obtained with 10 successful acquisitions and IQR/median > 30% were considered reliable [6]. Patients were classified into 3 groups according to baseline LSM (Baveno VI) [9].

- Group 1: Patients without compensated advanced chronic liver disease (cACLD) (*LSM* < 10 kPa)
- Group 2: Patients with suspected cACLD (*LSM* 10–15 kPa)
- Group 3: Patients with likely cACLD (*LSM* > 15 kPa)

Data collection and statistical analysis

The current study evaluated the effect of SVR using direct-acting antiviral (Sof/Dac) on the stage of liver fibrosis in HCV patients by measuring LSM using transient elastography before and after receiving treatment. Prior final analysis, data were screened for normality assumption test and homogeneity of variance. Data were normally distributed using Shapiro–Wilk test ($p > 0.05$) after removal of outliers detected by box and whiskers plots. Additionally, Levene's test for testing the homogeneity of variance revealed that there was no significant difference ($p > 0.05$).

All these findings allowed the researchers to conduct parametric and nonparametric analysis.

Statistical analysis was conducted using the Statistical SPSS Package program version 24 for Windows (SPSS, Inc., Chicago, IL, USA). The quantitative data descriptive

statistics included the mean and standard deviation for demographic data (age, weight, height, BMI), laboratory investigations, and LSM. Qualitative data descriptive statistics was used for distribution of number and percentage for gender, HBs Ag, HCV PCR, Child class, stage of fibrosis, and ultrasound (liver parenchyma, liver size, spleen size, and ascites) variables. The paired *t*-test was used to compare the means of laboratory investigations and LSM variables before and after treatment. The chi-square test (χ^2 test) was used to compare the distribution of Child class, stage of fibrosis, and ultrasound (spleen size and ascites) variables before and after treatment. Analysis of variance (ANOVA test) was used to compare laboratory variables before and after treatment across different stages of fibrosis. The Wilcoxon signed-rank test was used to compare subgroups within each liver stiffness category (< 10 kPa, 10–15 kPa, and > 15 kPa) in Table 3. All statistical analyses were significant at 0.05 level of probability ($P \leq 0.05$).

Results

All patients achieved SVR 24 with no significant side effects, and no patient was lost to follow-up. Baseline data and comparison of the demographic, clinical, and laboratory data among the 3 groups are shown in Table 1. They were 50 males (48.5%), with a mean age of 54.63 ± 10.42 years, mean BMI of 26.31 ± 3.33 kg/m^2, and 21 patients (20.4%) with type 2 diabetes. No patient had a history of excessive alcohol intake. All patients were classified as Child–Pugh score A.

A significant LSM decrease was observed at W24 compared to baseline in all patients (5.8 vs. 8.8 kPa, $p = 0.002$) as well as in the 3 groups of patients (group 1: 4.75 vs. 6.0 kPa, $p = 0.0001$; group 2 11.9 vs. 12.6 kPa, $p = 0.042$; group 3: 24.2 vs. 28.3 kPa, $p = 0.0001$). The overall decline in LSM in the 3 groups was 34.09% with 23.83% decline in group 1, 8.4% decline in group 2, and 14.31% decline in group 3 (Table 2) (Figs. 1, 2, 3 and 4). When LSM decrease after treatment was studied according to demographic data (age, gender, BMI, and type 2 diabetes) within the 3 groups of patients (Table 3), no difference was observed.

LSM decrease after treatment within the different groups according to biological data is shown in Table 4. A significant reduction of AST was observed in group 1 patients (from 45.91 ± 3.12 to 24.40 ± 8.43 U/l) and in group 3 patients (from 61.49 ± 6.07 to 37.25 ± 7.47U/l).

In group 1, ALT dropped from 51.54 ± 4.31 to 17.20 ± 9.80 U/l after treatment. In group 3 patients, it

Table 2 Comparison of the liver stiffness (LSM) between before and after treatment within each liver stiffness category

Liver stiffness	Before treatment	After treatment	Decline %	*p*-value
Total population	8.80 (5.80, 21.00)	5.80 (4.40, 12.60)	34.09%	0.002*
< 10 kPa	6.00 (3.6, 9.5)	4.57 (2.0, 9.8)	23.83%	0.0001*
10–15 kPa	12.60 (10.5, 14.8)	11.90 (10.1, 14.0)	8.40%	0.042*
> 15 kPa	28.30 (15.9, 67.8)	24.25 (15.4, 39.7)	14.31%	0.0001*

Data are expressed as median (interquartile range). *p*-value: probability value.
*Significant ($p < 0.05$)

Table 1 Baseline data

Variables	Liver stiffness				*p*-value
	< 10 kPa ($n = 54$)	10–15 kPa ($n = 17$)	> 15 kPa ($n = 32$)	Total ($n = 103$)	
Age (year)	50.91 ± 11.11	57.12 ± 8.41	55.88 ± 7.98	54.63 ± 10.42	0.183
Gender (male)	23 (22.3%): 31 (30.1%)	9 (8.7%): 8 (7.8%)	18 (17.5%): 14 (13.6%)	50 (48.5%): 53 (51.5%)	0.436
BMI	26.17 ± 3.29	25.87 ± 3.44	26.79 ± 3.37	26.31 ± 3.33	0.595
Diabetes	9 (8.7%)	4 (3.9%)	8 (7.8%)	21 (20.4%)	0.612
AST (U/L)	45.91 ± 3.12	56.24 ± 4.64	61.49 ± 6.07	52.46 ± 4.30	0.111
ALT (U/L)	51.54 ± 4.31	48.77 ± 9.36	53.37 ± 4.57	51.65 ± 8.82	0.926
Albumin (g/dL)	4.14 ± 0.43	3.92 ± 0.58	3.54 ± 0.67	3.92 ± 0.60	0.0001*
Bilirubin (mg/dL)	0.72 ± 0.36	0.78 ± 0.29	0.99 ± 0.38	0.82 ± 0.37	0.004*
INR	1.06 ± 0.08	1.10 ± 0.17	1.24 ± 0.28	1.12 ± 0.19	0.0001*
PLTs/μL	222,259 ± 65,665	233,000 ± 64,647	164,406 ± 62,332	206,058 ± 69,864	0.0001*
AFP (ng/mL)	5.01 ± 3.20	5.03 ± 2.96	12.23 ± 2.86	7.26 ± 2.25	0.0001*
FIB-4	2.27 ± 1.41	3.41 ± 3.09	4.72 ± 2.30	3.21 ± 2.31	0.0001*
Liver stiffness (kPa)	6.26 ± 1.62	11.95 ± 1.15	29.99 ± 12.09	14.57 ± 12.57	0.0001*

Numerical data are expressed as mean ± standard deviation, and categorical data are expressed as number (percentage)
p-value: probability value. *Significant ($p < 0.05$)

Table 3 Mean percent decrease of liver stiffness within each liver stiffness category according to demographic data using Wilcoxon signed-rank test

Liver stiffness	Variables	Patients groups	Number	Mean percent Liver stiffness change (%)	*p*-value*
< 10 kPa	Age	≤ 50 years	*n* = 23	− 25.69%	0.528
		> 50 years	*n* = 31	− 20.37%	
	Sex	Male	*n* = 27	− 21.17%	0.728
		Female	*n* = 27	− 24.11%	
	Diabetes	Nondiabetic	*n* = 40	− 19.71%	0.214
		Diabetic	*n* = 14	− 30.44%	
	BMI	BMI < 25	*n* = 16	− 30.74%	0.944
		BMI > 25	*n* = 38	− 30.84%	
10–15 kPa	Age	≤ 50	*n* = 5	− 18.59%	0.198
		> 50	*n* = 12	− 11.39%	
	Sex	Male	*n* = 9	− 18.64%	0.769
		Female	*n* = 8	− 7.73%	
	Diabetes	Nondiabetic	*n* = 14	− 22.93%	0.420
		Diabetic	*n* = 3	− 10.96%	
	BMI	BMI < 25	*n* = 9	− 39.38%	0.879
		BMI > 25	*n* = 8	− 39.59%	
> 15 kPa	Age	≤ 50	*n* = 13	− 22.72%	0.397
		> 50	*n* = 19	− 36.60%	
	Sex	Male	*n* = 14	− 26.88%	0.614
		Female	*n* = 18	− 34.14%	
	Diabetes	Nondiabetic	*n* = 27	− 30.63%	0.940
		Diabetic	*n* = 5	− 28.92%	
	BMI	BMI < 25	*n* = 11	− 33.33%	0.318
		BMI > 25	*n* = 21	− 31.14%	

also dropped from 53.37 ± 4.57 to 26.41 ± 2.90 U/l after treatment. A significant difference in INR was observed before and after treatment in group 1 patients. There was a statistically significant decrease of serum bilirubin in group 1 and group 2 patients before and after treatment. There was also significant improvement of Fib-4 in group 1 patients as it was (2.27 ± 1.41) and decreased to (1.54 ± 0.73) after treatment.

Discussion

HCV infection is a major cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide [5]. Egypt has the highest prevalence of HCV infection, a consequence of the prevalence of schistosomiasis and its mass treatment by unsafe intravenous injections in the 1950s to 1980s [3]. In DHS (2017), the percentage of adults (15–59 years old) testing positive for the HCV RNA test is 7% of the Egyptian population [2]. A lower seroprevalence of HCV in Egyptian patients (4.61%) has been recorded following the huge screening and treatment campaign performed in 2018 and 2019 [3]. The treatment of HCV nowadays depends on DAAs. This interferon-free DAA therapy has revolutionized antiviral therapy in hepatitis C so that successful hepatitis C treatment can be offered to virtually all patients irrespective of their comorbidity [10].

One of these regimens is the sofosbuvir plus daclatasvir (SOF/DAC), with or without ribavirin, which was widely used in Egypt according to the National Committee for Control of Viral Hepatitis (NCCVH) [11]. The availability of the low-cost local generics allowed the treatment of large numbers of patients and achieved a great success. Although HCV genotype 4 was considered the "most difficult to treat" genotype, the introduction of new DAAs therapy resulted in a significant improvement of SVR rates, over 90% [12]. Genotyping was not performed at baseline in the present study, not being a prerequisite for antiviral therapy according to the national treatment protocol in Egypt. However, more than 90% of patients in Egypt are infected with HCV genotype 4 in many published reports, and this report can thus be taken to represent results of HCV genotype 4 treatment [13]. Interestingly, SVR24 was observed in all patients, and no patient was lost to follow-up.

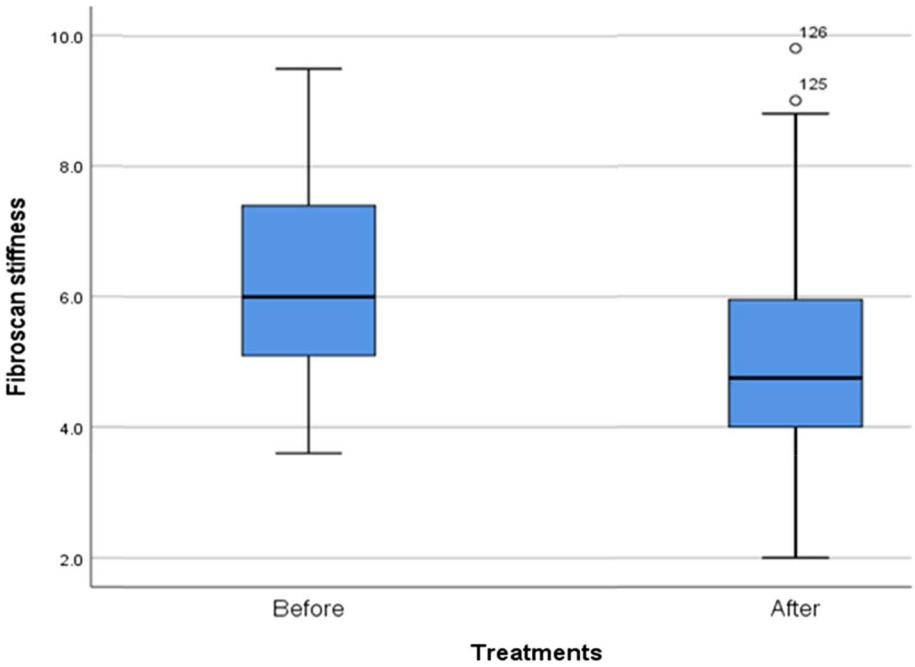

Fig. 1 The liver stiffness Boxplot between before- and after-treatment within < 10 KPa category

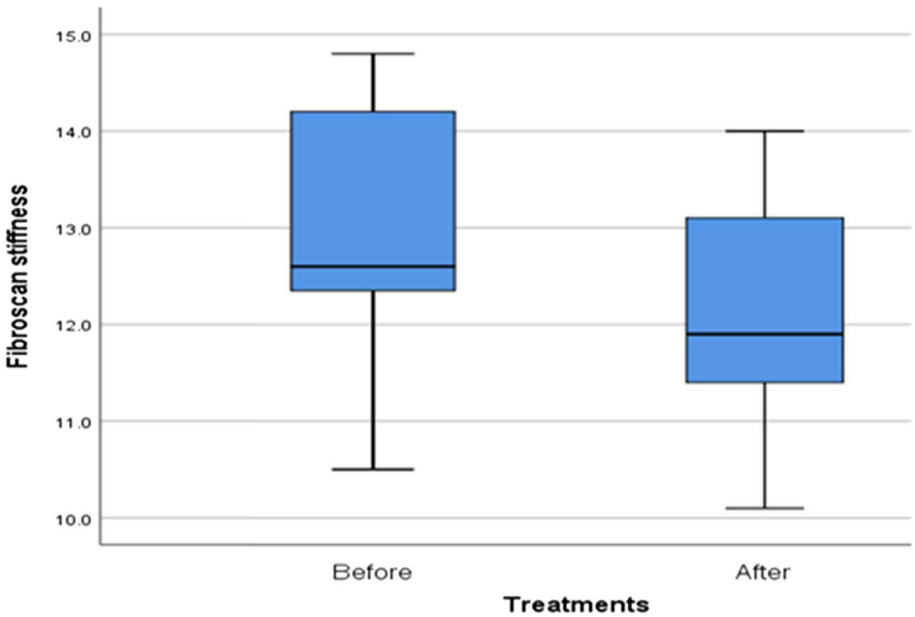

Fig. 2 The liver stiffness Boxplot between before- and after-treatment in patients within < 10 KPa category

Our study included 103 chronic hepatitis C infection patients who received SOF/DAC for 12 weeks and were assessed before and 24 weeks after receiving treatment (SVR-24). The total number of our patients as well as their age are comparable to those in studies by Tagadeen et al. [14], which included 80 patients with genotype 4 HCV infection, and Chan et al. [15], which included 70 HCV patients with different genotypes.

Our study showed, as expected, a significant reduction of AST and ALT, a finding in agreement with those of other studies [14–17]. Also, a significant improvement in FIB-4 was observed in this study as previously reported

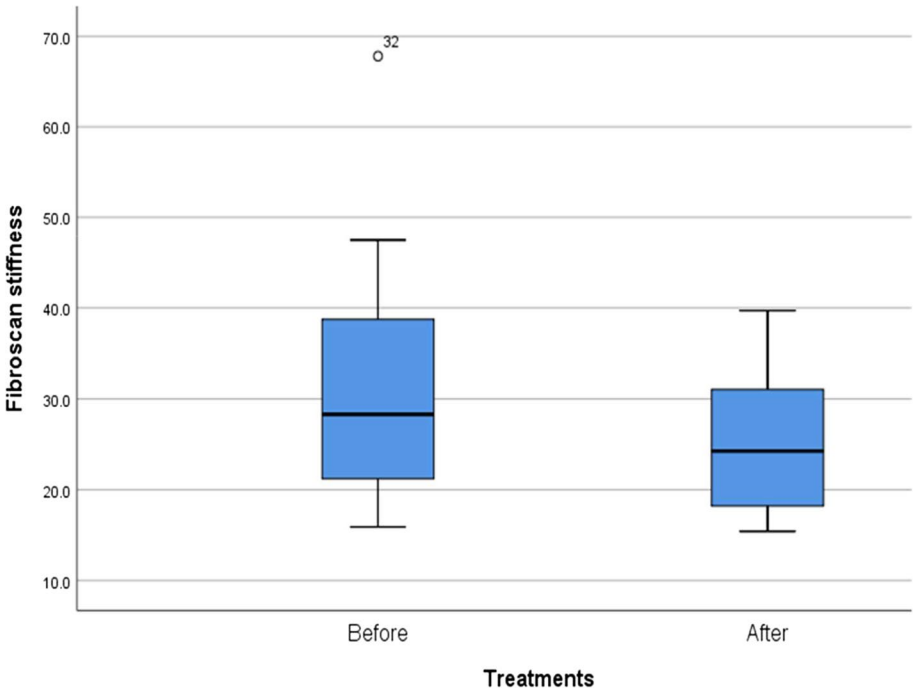

Fig. 3 The liver stiffness Boxplot between before- and after-treatment in patients within 10 - 15 KPa category

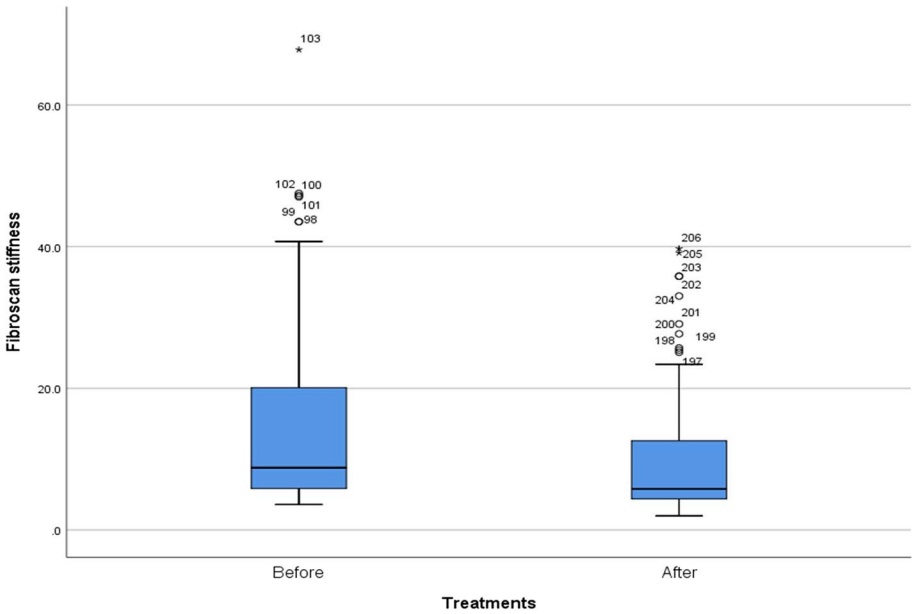

Fig. 4 The liver stiffness Boxplot between before- and after-treatment in patients within > 15 KPa category

by Persico et al. [16] and Tagadeen et al. [14]. The decline in FIB-4 values might primarily result from reduction in necro-inflammation as evidenced by decreased ALT levels. Hsu et al. [17] assumed that the change of FIB-4 values might be due to the rapid decline in AST and ALT levels and to a lesser extent increased platelet count.

We classified our patients into 3 groups according to LSM for the presence or absence of compensated advanced chronic liver disease (cACLD) according

Table 4 Comparison of the lab investigations between before and after treatment within each liver stiffness category

Variables	Liver stiffness	Before treatment	After treatment	Improvement %	*p*-value
AST (U/L)	< 10 kPa	45.91 ± 3.12	24.40 ± 8.43	46.85%	0.0001*
	10–15 kPa	56.24 ± 4.64	39.64 ± 2.83	29.52%	0.168
	> 15 kPa	61.49 ± 6.07	37.25 ± 7.47	39.42%	0.002*
ALT (U/L)	< 10 kPa	51.54 ± 4.31	17.20 ± 9.80	66.63%	0.0001*
	10–15 kPa	48.77 ± 9.36	32.19 ± 9.62	34.00%	0.161
	> 15 kPa	53.37 ± 4.57	26.41 ± 2.90	50.52%	0.001*
Albumin (g/dL)	< 10 kPa	4.14 ± 0.43	4.13 ± 0.32	0.24%	0.827
	10–15 kPa	3.92 ± 0.58	4.06 ± 0.30	− 3.57%	0.397
	> 15 kPa	3.54 ± 0.67	3.75 ± 0.41	− 5.93%	0.163
Bilirubin (mg/dL)	< 10 kPa	0.72 ± 0.36	0.51 ± 0.36	29.17%	0.002*
	10–15 kPa	0.78 ± 0.29	0.53 ± 0.14	32.05%	0.005*
	> 15 kPa	0.99 ± 0.38	0.81 ± 0.27	18.18%	0.174
INR	< 10 kPa	1.06 ± 0.08	1.11 ± 0.10	− 4.72%	0.002*
	10–15 kPa	1.10 ± 0.17	1.41 ± 0.68	− 28.18%	0.167
	> 15 kPa	1.24 ± 0.28	1.29 ± 0.22	− 4.03%	0.484
PLTs/μL	< 10 kPa	222,259 ± 65,665	277,833 ± 559,642	− 25.00%	0.406
	10–15 kPa	233,000 ± 64,647	248,363 ± 257,346	− 6.59%	0.850
	> 15 kPa	164,406 ± 62,332	132,650 ± 54,319	19.32%	0.059
AFP (ng/mL)	< 10 kPa	5.01 ± 3.20	3.38 ± 2.97	32.53%	0.004*
	10–15 kPa	5.03 ± 2.96	4.25 ± 3.50	15.51%	0.547
	> 15 kPa	12.23 ± 2.86	8.48 ± 1.38	30.66%	0.168
FIB-4	< 10 kPa	2.27 ± 1.41	1.54 ± 0.73	32.16%	0.001*
	10–15 kPa	3.41 ± 3.09	2.76 ± 1.83	19.06%	0.491
	> 15 kPa	4.72 ± 2.30	3.81 ± 2.60	19.28%	0.206

Data are expressed as mean ± standard deviation. *p*-value: probability value. *Significant ($p < 0.05$)

to Baveno VI criteria [9]. A significant LSM decrease was observed at W24 compared to baseline in the 3 groups of patients, and no patients had stable or worsening reading of LSM, a finding in keeping with those of previous studies [14–17]. Group 1 had the highest LSM decline (23.83%), followed by group 3 (14.3%) and group 2 (8.4%). Nevertheless, it should be kept in mind that LSM does not only reflect fibrosis and may be also affected by inflammation in the liver [9, 18]. Liver fibrosis regression is not guaranteed to take place upon treating the offending agent. Many factors had been demarcated to be of influence on the occurrence of the fibrosis regression process: age of the individual, genetic and epigenetic factors, rate of fibrosis progression (slow or rapid fibrosis), or disease-related factors like etiology and staging of chronic liver disease [19–23]. All these studies have raised significant concern about the credibility of all used parameters in the genuine assessment of fibrosis regression, or these are the penalties of alleviated necro-inflammation following the direct viral effects of these drugs. So, despite the marvelous achievement of the therapeutic goal of DAAs, more meticulous judging measures are still needed for better appraisal of the proposed residual liver disease burden following the end of therapy [24].

Conclusion

HCV eradication was associated with a significant LSM decrease in all groups of patients. This is likely related to fibrosis improvement, but its relation to necro-inflammatory improvement cannot be excluded. Longer follow-up of fibrosis in these patients is needed.

Authors' contributions

All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare that they have no competing interests.

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